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Abstract: Asphyxia may cause a hypoxic-ischemic encephalopathy due to an insufficient supply of oxygenated blood to the brain,which leads to a cerebral palsy. The transition state between both is called neonatal encephalopathy. However, there are many other causes for neonatal encephalopathy, such as developmental abnormalities, metabolic abnormalities, autoimmune disorders, coagulation disorders, infections, trauma, IUGR, and chromosomal abnormalities. Therefore, the American College of Obstetricians and Gynecologists defined criteria, sufficient for an acute intrapartum event to cause a cerebral palsy. Asphyxia itself causes a redistribution of the blood flow towards the central organs, the brain and heart, but in a further stage the cerebral energy metabolism may breakdown and a cascade of events will occur: energy, i.e. ATP, fails for Na+/K+ pumps, the gradients of Na+/K+ across the cell membranes cannot any longer be maintained and cell oedema develops, furthermore, glutamate is released and exerts a neurotoxic influence, Ca2+ overflows the cells and activates lipases, proteases and nucleases, the cellular protein synthesis decreases, after the insult reperfusion of the tissue occurs, but oxygen radicals with a nefast influence are formed, interleukins are released and an inflammatory reaction takes place and proto-

oncogenes are expressed. Cell death is an inevitable consequence, leading to the hypoxic-ischemic encephalopathy.

Hypoxic-ischemic encephalopathy: facts and insights

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Abstract: Asphyxia may cause a hypoxic-ischemic encephalopathy due to an insufficient supply of oxygenated blood to the brain, which leads to a cerebral palsy. The transition state between both is called neonatal encephalopathy. However, there are many other causes for neonatal encephalopathy, such as developmental abnormalities, metabolic abnormalities, autoimmune disorders, coagulation disorders, infections, trauma, IUGR, and chromosomal abnormalities. Therefore, the American College of Obstetricians and Gynecologists defined criteria, sufficient for an acute intrapartum event to cause a cerebral palsy.
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Hypoxic-ischemic encephalopathy in its clinical context

During intrauterine asphyxia, severe fetal brain damage due to neuronal death may occur, which is named hypoxic-ischemic encephalopathy (HIE). Thereafter, cerebral palsy (CP) becomes apparent as a chronic disability of CNS origin: there is aberrant control of movement and posture, starting early in life, which is not linked to neurological disease. The estimated CP rate is 1.5 per 1000. CP remained fairly constant over the last 30 years, although the percentage of caesarean sections increased dramatically. The classical markers for asphyxia, such as meconium, fetal monitoring with decelerations and/or tachycardia and a low Apgar score proved to be false positive in 99.8% for the subsequent development of CP. Asphyxia and HIE do not result directly in CP: the transition state is called neonatal encephalopathy, a clinically defined syndrome of disturbed neurological function in the infant at or near term during the first week after birth, manifested by difficulty with initiating and maintaining respiration,

depression of tone and reflexes, altered level of consciousness, and often seizures. Neonatal encephalopathy occurs in 1.8 to 7.7 per 1000 term deliveries and in many cases no CP develops.
The differential diagnosis of neonatal encephalopathy is large: developmental abnormalities, metabolic abnormalities, autoimmune disorders, coagulation disorders, infections, trauma, hypoxia, IUGR, multiple gestations, antepartum hemorrhage, chromosomal abnormalities (1, 2). The insult may be ante- or intrapartum and even neonatal. Badawi et al. (1, 2) found that risk factors for neonatal encephalopathy were in 69% ante partum, in 25% ante partum and due to intrapartum hypoxia, in 4% due to intrapartum hypoxia, and in 2% unknown.
Therefore, the several possibilities for neonatal encephalopathy and the timing of the insult should be considered when a neonate in poor condition is born. However, the obvious reflex in such a case is rather to think in terms of asphyxia. Suspicions about bad obstetrical care were frequent, and convictions by expert obstetricians have not been unusual. A study by Hankins (3) demonstrated the lack of basic knowledge among obstetricians about this item. In 2003 a task force from the American College of Obstetricians and Gynecologists (ACOG) defined following criteria (based on the criteria of the International Cerebral Palsy Task Force; (4)) for an acute intrapartum event to be sufficient to cause a cerebral palsy (5):
Essential criteria (must meet all four)

1. Evidence of a metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH <7 and base deficit =12 mmol/l or more)
2. Early onset of severe or moderate neonatal encephalopathy in infants born at 34 or more weeks of gestation
3. Cerebral palsy of the spastic quadriplegic or, less commonly, dyskinetic type
4. Exclusion of other identifiable etiologies such as trauma, coagulation disorders, infectious conditions, or genetic disorders

Criteria that collectively suggest an intrapartum timing (within close proximity to labor and delivery, e.g., 0-48 hours) but are nonspecific to asphyxial insults

1. A sentinel (signal) hypoxic event occurring immediately before or during labor, such as umbilical cord prolapse.
2. A sudden and sustained fetal bradycardia or the absence of fetal heart rate variability in the presence of persistent, late, or variable decelerations, usually after a hypoxic sentinel event when the pattern was previously normal
3. Apgar scores of 0-3 beyond 5 minutes
4. Onset of multisystem involvement within 72 hours after birth
5. Early imaging study showing evidence of acute nonfocal cerebral abnormality

Pathophysiology of hypoxic-ischemic encephalopathy

Hypoxia results from an insufficient fetomaternal gas exchange, usually secondary to an arrest of uteroplacental blood flow or umbilical cord occlusion. By the sympathetic-adrenergic nervous system the fetus reacts immediately. There is a blood flow

redistribution in the fetus: peripheral organs are less perfused, whereas the perfusion of the fetal brain and heart is kept upright as long as possible. But when hypoxia is severe or continues, then oxygen as a drive for the oxidative phosphorylation starts to fail. Lactate is produced from glucose by anaerobic glycolysis, and a metabolic acidosis may develop. A further step is the breakdown of energy metabolism, which may happen in the cerebral cortex within a few minutes. ATP gets exhausted and the ionic pumps can not any longer maintain the gradients for Na^+, K^+ and Ca^{2+} across the cell membranes. Water flows into the cells and cell oedema develops as a consequence. Furthermore, the increase in intracellular Ca^{2+} will activate enzymes, such as lipases, proteases and nucleases, causing further cell damage. The release of the neurotransmitter glutamate is a additional neurotoxic element during hypoxia. If the fetus manages to survive the hypoxic insult, but the brain has come to a standstill, then reperfusion of the brain will deliver oxygen and also oxygen radicals, causing further neuronal damage. Protein synthesis is inhibited, proto-oncogenes are expressed, and inflammatory reactions with the expression of cytokines occur. Cell death is the consequence, leading to the hypoxic-ischemic encephalopathy.

One should realise, however, there is only a narrow window during asphyxia between intact survival and fetal death, with HIE in between. During moderate hypoxia, survival is not endangered, but fetal development and growth is adapted (6, 7).

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